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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SINGH, ANOOP KUMAR	
ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/589,589	HIGH ET AL.	
	Examiner	Art Unit	
	ANOOP SINGH	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 August 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,24,28,43 and 44* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-2, 24, 28, 43 and 44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendments and response filed August 26, 2008 has been received and entered. Claims 3-23, 25-27, 29-42 have been canceled. Applicants have also added claim 44 generally directed to elected invention. Claims 1-2, 24, 28, 43 and 44 are pending in the instant application.

Maintained- Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-2, 24, 28 and 43 remain rejected under 35 U.S.C. 112, first paragraph and newly added claim 44 is also rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicants' arguments filed August 28, 2008 have been fully considered but are not persuasive. Applicant argues that that engaging in experimentation to practice a claimed invention does not render the disclosure non-enabling as long as the experimentation required is not "undue" (See page 5 of the arguments). Applicants also assert that the Examiner has relied almost exclusively on post filing references which disclose a later existing state of the art in order to arrive at the instant enablement rejection.

In response, it is noted that contrary to applicants' assertion examiner has provided state of art with respect to unpredictable nature of gene delivery and

therapy prior and after filing of this application. In fact, gene delivery and gene therapy prior to filing of this application was unpredictable as numerous factors complicated the gene delivery art that is difficult to be overcome by routine experimentation. These factors differ significantly based on the vector used and the protein being produced (Ecke, Goodman & Gilman's The Pharmacological basis of Therapeutics, 1996, McGraw-Hill, New York, NY. pp 77-101, art of record). These observations were further supported by post filing art of Walsh (Gene Therapy, 2003, 10, 999-1003) who while reviewing the state of gene therapy in hemophilias states "AAV2 vectors carrying human factor IX cassettes delivered via the hepatic artery resulted in lower level of expression" (see page 1001, col. 2, para. 2). In fact, the study concludes that a review of the preclinical data suggests that animal studies may not be predictive of the outcome in humans. Walsh specifically discloses that vector dosing based on a vector particle-to-weight ratio produced discrepant results when comparing equivalent AAV vector dosing in mice and hemophilic dogs. Recent data testing AAV2/human factor IX vectors in non-human primates produced 4–10% factor IX, similar to data generated in hemophilic dogs for a period of 1 year. Walsh asserts that these preclinical outcomes reflect that species differences in terms of rate of infectivity, gene expression, protein modification and processing (see page 1001, col. 2, last para.). The specification does not provide nexus between the data obtained in rodent and canine model by delivering specific serotype of AAV via a specific route to similar effect in other species using AAV of other serotype via any route as embraced by the breadth of the claims. Thus, in view of forgoing it is apparent that reservation expressed by Ecke with respect to the fate of vector itself, volume of distribution, rate of clearance and resulting effect in tissue or a target organ was not fully resolved in even after filing of this application. It is reasonable to assert that the unpredictability in the animal studies (see Walsh, above), one of skill in the art could not rely upon the art to predictably achieve hemophilia gene therapy in humans. MPEP 2164.05(a) states "If

individuals of skill in the art state that a particular invention is not possible years after the filing date, that would be evidence that the disclosed invention was not possible at the time of filing and should be considered. In *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513-14 (Fed. Cir. 1993). Given differences in the outcome of expression level in different species, particularly when taken with the lack of guidance in the specification, it would have required undue experimentation to establish the levels of the transgene expression, the consequences of that expression, and therefore, the resulting effect in treating the deficiency of Factor IX in any subject, as embraced by the breadth of the claims.

Applicant argues that Applicants have previously submitted data which clearly demonstrates that, in a canine model, the administration of cyclophosphamide with Factor IX gene therapy was effective at "preventing the formation of inhibitory antibodies to Factor IX", as instantly claimed (see October 23, 2006 Official Action response and Exhibit A provided therewith). Applicants assert that no inhibitory antibodies against FIX were detected in all the dogs which received cyclophosphamide with FIX gene therapy (Arruda et al. (Blood (2005) 105:3458-3464). Applicant agues that effectiveness of claimed methods on different animals indicates that instant claims are enabling and do not require undue experimentation.

In response, as an initial matter it is noted that breadth of the claims embrace administering using any dose and serotype of AAV that could be delivered for the treatment of hemophilia B and prevention of formation of inhibitory antibodies to Factor IX, any site of administration to affect genetic defect caused by the lack of Factor IX. It is noted that art teaches that dose of vector and level of transgene expression may determine whether antibodies are transient or persistent (see Arruda et al Blood, 2004, 103(1) 85-92page 85, col. 2, last two lines). Arruda discloses that the combination of dose reduction and transient immuno suppression by cyclophosphamide initially appeared successful, however, three weeks after

cyclophosphamide therapy the animal developed a bleed in the hindlimb (See page 91, col. 1, last para. to col. 2, para. 1). Furthermore, contrary to applicants' assertion the teaching of Arruda et al (Blood. 2005) clearly shows that method of gene delivery in hemophilia is critical to the resulting outcome in patient. The specification fails to provide nexus between direct injections of vector to different delivery method described in Arruda. Given that the outcome of expression level in different species, particularly when taken with the lack of guidance in the specification with respect to intravascular gene delivery method, it is reasonable to state that one of ordinary skill in the art would have to perform undue experimentation to determine appropriate serotype and gene delivery method of AAV in the treatment of hemophilia B without reasonable expectation of success.

Applicants also provide the reference of Jiang et al (Molecular Therapy (2006) 14:452-455) in support of instant claims showing that the results from a phase I clinical trial of FIX gene therapy on humans. Applicants assert finding of Jiang et al clearly shows that claimed methods are enabling (page 8 of the argument).

In response to applicant's argument with respect to Jiang's reference, it is noted that Jiang uses administration of an AAV2-FIX vector into the skeletal muscle of the subject. The features upon which applicant relies (i.e., AAV-2 or intramuscular administration of vector and specific dose of AAV) are not recited in the rejected claims. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. It is emphasized that claims read on administering any dose, route and serotype of AAV along with intravenously or intraperitoneally administering to the mammal cyclophosphamide prior to or simultaneously. The results of Jiang only provide guidance with respect to multiyear FIX expression by AAV2 vector in humans and only suggest that improved muscle delivery provides effective treatment for protein deficiencies or muscle-specific diseases. In the instant case, claims are broad and do not limit to any specific route or serotype of AAV for the treatment of Factor IX deficiency.

Applicants assert that the Subject H in Jiang's reference reported a decrease in bleeding episodes, thereby indicating that the administration of FIX via an AAV vector (gene therapy) resulted in a correction/amelioration of the hemophilic bleeding condition (see page 453).

In response, it is noted applicants only provide selective teaching of Jiang. In fact, Jiang et al further reported that the decrease in bleeding of Subject H is anecdotal and may be a placebo effect (emphasis added, see page 453, col. 1, para. 2). Further, Jiang et al state"[i]t precipitated the speculation that Subject H may be synthesizing FIX at some low level, i.e., 1% of normal (ranging from 0.3 to 0.8%). Therefore, applicant's assertion that Jiang et al report a decrease in bleeding episode by delivering AAv of serotype 2 is premature and was not fully resolved even several years after filing of this application. Given the broadest reasonable interpretation in view of the instant specification Examiner had previously indicated that the only intended purpose of delivering adeno-associated viral (AAV) vector in any mammal was to treat/correct Factor IX deficiency. Applicant should note that "case law requires that the disclosure of an application shall inform those skilled in the art how to use applicants' alleged discovery, not to find out how to use it for themselves." *In re Gardner* 166 USPQ 138 (CCPA) 1970. An artisan would have to perform undue experimentation to make and use invention without reasonable expectation of success.

Applicants argue that the reference of Kaiser is irrelevant to the claimed method, while Chao shows that rAAV1 vectors may bring about a dramatic increase in FIX expression after transducing skeletal muscle in large animal models (see page 9 of the arguments).

In response, it is noted that the reference of Kaiser was included to demonstrate that although several patients have safely received AAV since 1992. However, Kaiser discloses that patient receiving more than one raises the possibility that the patient became sensitized to the vector, leading to an adverse

reaction and a mild immune reaction. The failure of AAV based gene therapy raises the unpredictable fate of vector, volume of distribution, rate of clearance in tissue, the *in vivo* consequences of altered gene expression and protein function in an subject for treating any condition by delivering viral vector (AAV) comprising therapeutic gene. In the instant case, claims do not limit to any specific serotype of AAV gene delivery system for correcting hemophilia B. However, Chao et al disclose, it is reasonable to hypothesize that virus binding and entry into the target cells, intracellular trafficking and nuclear transportation, all of which are associated with the unique capsid of the AAV serotypes, may be the major machinery accounting for significant differential transgene (cFIX) expression efficiency of AAV serotype vectors. An artisan would have to perform undue experimentation to make and use the invention without reasonable expectation of success.

With respect to applicants' argument of misquote of Walsh reference, it is noted that contrary to applicants' assertion Walsh summarizes the outcome of previous studies that reflect species differences in terms of the rate of cell infectivity, gene expression, protein modification and processing (see page 1001, col. 2, last line to page 1002, col. 1). In fact, Walsh only reviews the preclinical data to suggest that animal studies may not be predictive of the clinical outcome. For example, vector dosing based on a vector particle-to-weight ratio produced discrepant results when comparing equivalent AAV vector dosing in mice and hemophilic dogs (see page 1001, col. 2, last para.).

Applicants' argument of improvement of FIX levels to at least 1% of normal in humans results in the improvement of normal in humans results in the improvement of hemophilic symptoms (see Lofqvist et al, argument page 10), it is noted that applicants have not provided evidence to suggest that at least 1% FIX level could be achieved by delivering AAV of different serotype via any route (i.e oral, intranasal, intramuscular, intravenous, subcutaneous etc.) to any subject such

that factor IX deficiency is corrected. It has been difficult to predict the efficacy and outcome of transduced therapeutic gene because several factors govern the expression and/or therapeutic potential of transduced gene *in vivo*. As stated before it has been difficult to predict the efficacy and outcome of transduced therapeutic gene because several factors govern the expression and/or therapeutic potential of transduced gene *in vivo*. The transduction of target cells will not only depends upon the type of target cells but also on the choice and/or characteristics of delivery vectors (as discussed before, supra).

Applicants' ague that specification need not contain working example if the invention is otherwise disclosed such that one skilled in the art could practice it without undue experimentation. Applicants assert that contrary to Examiner specification refers to other references that describe dosing and route of administration for AAV vector encoding FIX (page 11 of the arguments). Applicants also argue that references of Arrudda et al (Blood, 2005, 105 85-92) do not teach that intravenous procedure will be sub effective. Applicant also asserts that Arruda (Blood, 2004, 85-92) shows that claimed method are enabling. Further, applicants also argue that Ponder and Manno are irrelevant to instant enablement (see pages 12 and 13).

In response, contrary to applicants' assertions, the title of section referred by examine itself states" peripheral intravenous delivery of rAAV to a hemophilia B dog results in sub therapeutic FIIX level (emphasis added, see page 3461, col.2, para. 3). Arruda et al states "hemophilic animal was infused by peripheral vein with AAV-CMV-cFIX at a dose of 2.9 X 10^{12} vg/kg, accompanied by short-term administration of cyclophosphamide and MESNA. The resulting level of F.IX was approximately 50 ng/mL, or approximately 1% of normal circulating levels (Figure 3A), with a corresponding absence of positive fibers on muscle biopsy (Figure 5G). Thus it seems unlikely that the procedure will be successful as a simple intravenous infusion, at least with this AAV serotype". The reference was applied to show that

resulting effect of expression level in different species is critically dependent upon the route of administration and serotype of AAV. Similarly, Arruda et al (Blood, 2004, 103(1) 85-92) is applied to show that transient immuno suppression with cyclophosphamide could prevent inhibitor formation in dogs treated at higher doses and in nonsense mutation dogs. However, Arruda teaches that the combination of dose reduction and transient immunosuppression by cyclophosphamide initially appeared successful; however, three weeks after cyclophosphamide therapy the animal developed a bleed in the hindlimb (see page 89, col.2, and last para.). The reference is applied to shows that it is noted that applicants' own work after several years after filing of this application list some of the factors that influence the risk of inhibitor formation in the setting of gene transfer including "[u]nderlying mutation, the vector itself, the route of administration, the presence or absence of a tissue-specific promoter, and the dose" (See page 91, col. 1, last para. to col. 2, para. 1). With respect to Ponder reference, it is emphasized that it is applied to support the teaching in prior as well as post filing art regarding varying effect depending on type of vector used for gene delivery (see Ecke, Walsh, Arruda, all art of record, supra). Ponder cites other references to indicate that neither AAV6 nor AAV8 vectors are more effective than AAV2 at expressing canine FVIII in dogs with hemophilia A in one study, however, in an other study, expression of canine FIX from an AAV8 vector was 2-fold that from an AAV2 vector in dogs with hemophilia B, while expression from AAV5 was lower than that from AAV2 (see page 303, entire col. 2). These studies clearly indicate that different capsid protein from AAV serotype have different expression pattern and subject to variable biological effect. Given that the outcome of expression level in different species, particularly when taken with the lack of guidance in the specification with respect to intravascular gene delivery method using any serotype of AAV, it is reasonable to state that one of ordinary skill in the art would have to perform undue experimentation to determine

appropriate serotype and gene delivery method of AAV in the treatment of hemophilia B.

Lastly, Applicants argue that the Office is inappropriately imposing on the requirements for patentability the standards used to evaluate a drug product for clinical use. Requiring data from human clinical trials to satisfy the enablement requirement is outside the domain of the Office Applicants assert that immunosuppression is useful to prevent inhibitory antibodies to the gene being delivered to a patient (see page 14 and 15)..

In response, it is emphasized that Examiner has no intention to raise imposing on the requirements for patentability the standards used to evaluate a drug product for clinical use. The enablement rejection is made in view of In re Wands and issues raised herein are intended to address unpredictable nature associated with respect to gene delivery and therapy as observed by many different investigators (see art of records). Furthermore, it was clearly indicated in previous office action that although instant claims are directed to a method of preventing the formation of inhibitory antibodies to Factor IX delivered to a mammal by way of an adeno-associated viral (AAV) vector, they were analyzed for their intended effect on correcting hemophilia B in any mammal by delivering to any site and any dose of AAV comprising factor IX. Examiner has clearly shows that prior art as well as numerous post filing art show AAV of different serotype at different dose delivered via different route has variable effect. In view of breadth of the claims and absence of adequate showing by Applicant, in the way of specific guidance and direction, and/or working examples demonstrating the same, such invention as claimed by Applicant is not enabled for the claimed inventions. The specification and prior art do not teach a method of preventing the formation of antibodies by administering cyclophosphamide prior or simultaneously with plurality of different serotype of AAV comprising gene encoding Factor IX delivered via any route to exert intended therapeutic effect. An artisan of skill would have required undue experimentation

to practice the method as claimed because the art of gene delivery intended for gene therapy, with the intended use for humans, with any AAV comprising gene encoding FIX was unpredictable at the time of filing of this application as supported by the observations in the art record.

Conclusion

No Claims allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Smith et al (Gene Therapy (1996), 3(6), 496-502) and Dwarki et al (WO9906562).

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ANOOP SINGH whose telephone number is (571)272-3306. The examiner can normally be reached on 9:00AM-5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272- 4517. The fax

phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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